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Estimating Toxicity Pathway Activating Doses for High Throughput Chemical Risk Assessments

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Estimating a Toxicity Pathway Activating Dose (TPAD) from *in vitro* assays as an analog to a reference dose (RfD) derived from *in vivo* toxicity tests would facilitate high throughput risk assessments of thousands of data-poor environmental chemicals. Estimating a TPAD requires definition of biological pathways leading to specific adverse effects, and development of *in vitro* assays for these pathways that can rapidly, efficiently and quantitatively test large sets of chemicals. The ToxCast and Tox21 programs are providing data from hundreds of *in vitro* assays, on thousands of environmental chemicals. The first step is to estimate minimum chemical concentrations required to significantly perturb biological pathways *in vitro*, i.e., the Toxicity Pathway Activating Concentration (TPAC). Toxicokinetic modeling is then used to estimate the *in vivo* oral dose required to achieve the TPAC as an internal dose in the target species (e.g., human serum concentration). Uncertainties are incorporated in both the TPAC and the toxicokinetic parameters, and these are combined to yield a probability distribution for the dose required to activate the pathway. The TPAD is defined as the lower, protective end of this pathway-activating confidence interval. We illustrate with two examples. In the first case, TPADs and RfDs corresponding to liver pathology for 13 conazole fungicides are compared. In most cases, TPAD values are lower than RfDs, and so provide a reasonable starting point for setting safe exposure limits for data poor chemicals. In the second case, the lowest TPADs for any pathway are compared with RfDs for a set of 35 chemicals and, again, were mostly found to be lower than RfDs. TPADs are significantly higher than RfDs (less protective) in a few cases, but most of these are cholinesterase inhibitors, where bioactivation is required for toxicity. This abstract does not necessarily reflect Agency policy.